The bioactivation of drugs chemicals to chemically reactive intermediates and their covalent binding to proteins is widely implicated in chemical toxicity.

Target-organ toxicity is often the consequence of the covalent binding of reactive metabolites to protein targets, but relevance of specific protein targets and the downstream mechanisms that finally result in organ damage or failure has not been defined. Although many protein targets for reactive drug metabolites have been identified, the role of covalent binding in toxicity is difficult to generalize since covalent binding may lack apparent toxic consequences or may be associated with major organ damage. Although the covalent binding of reactive intermediates generated by biotransformation of drugs or chemicals is a key initial event in chemical-induced toxicity, the biological mechanisms by which the covalent modification of proteins induces cell damage and death are still poorly understood.

Low-incidence, drug-induced organ toxicity is a major cause of market withdrawals of approved drugs. Such low-incidence effects (“idiosyncratic” toxicities) are difficult to predict in preclinical toxicity screening, and the role of covalent binding in low-incidence drug toxicity is not well defined. Although the downstream events that follow bioactivation to a reactive metabolite are poorly understood, target-organ toxicity, specifically liver toxicity, is often associated with the bioactivation of a drug or chemical to a reactive electrophilic metabolite.